3.24 Chemistry of Cannabis

Arno Hazekamp, Justin T. Fischedick, Mónica Llano Díez, Andrea Lubbe, and Renee L. Ruhaak,
Leiden University, Leiden, The Netherlands

3.24.1   An Introduction to the Cannabis Plant

Almost no plant has been studied as much as the Cannabis plant (*Cannabis sativa* L.); more than 10 000 papers have been published describing various aspects of Cannabis as a biologically active plant. Nonetheless, it is hard to think of a medical topic that can so strongly divide the research community as the medicinal use of Cannabis. It may even be stated that Cannabis is the most controversial plant in the history of mankind. But imagine if *C. sativa* were to be discovered today, growing in some remote spot of the world, it would be hailed as a wonder of nature; a new miracle plant with the potential to treat anything ranging from headaches to neurological disorders to cancer. Still, the potential of Cannabis was largely ignored until the discovery of the human endocannabinoid system, about a decade ago. Nowadays, it is known that many of our own body functions are controlled by Cannabis-like substances in our brain, immune system, and other organs.

But Cannabis plants are interesting to human society in more ways. As a fiber plant, Cannabis produces some of the best and most durable fibers of natural origin, historically used to produce ropes and sails for sea ships, paper, banknotes, and even the first Levi's jeans. Modern applications include dashboards for exclusive cars and insulation for houses. The oil of the hempseed was found to be well balanced with regard to the ratio of omega-3- to omega-6 fatty acids for human nutrition, and can be used as a sustainable alternative to fish oil. Furthermore, the oil is ideal as an ingredient for body oils and lipid-enriched creams.

The medicinal use of Cannabis has a very long history. However, the availability of alternative treatments, absence of quality control, and sociopolitical pressure led to a decline in the medical use of Cannabis by the beginning of the twentieth century. As a result, in the past decades its medicinal potential continued to be disputed. But despite its illegality, people have continued to obtain Cannabis on the black market for self-medication.

At least one bioactivity of Cannabis is undisputed: the psychoactive effect of delta-9-tetrahydrocannabinol (THC) is one of the best-studied biological activities in the world. As a result, the attention has shifted from the Cannabis plant as a whole, to its main psychoactive component. Interestingly, THC, a terpenophenolic compound, contains no nitrogen atom and therefore is not an alkaloid, which is rare among the psychotropically active compounds. Furthermore, therapeutically used THC is among the most nonpolar compounds used in medicine today. Chemically, THC belongs to a group of closely related compounds known as cannabinoids, and they are considered the main bioactive components of Cannabis. Up to date, already 70 different cannabinoids have been described, several of which were found to be bioactive in one or more ways.

Cannabis has the potential to evolve into useful and much needed new medicines, but this is seriously obstructed by its classification as a dangerous narcotic. But as shown in the case of the poppy plant (*Papaver somniferum*) and the opiates derived from it (e.g., morphine, codeine), the distinction between a dangerous drug of abuse and a medicine can be made by proper, unbiased, and well-conducted research, combined with a rational approach. Relevant biological activities, as shown by thorough research in the laboratory, and finally confirmed through properly conducted clinical trials, are the best guarantee for the future of Cannabis as a medicine. The information presented in this chapter should help researchers of various disciplines to understand the current scientific status of the Cannabis plant and its constituents.

3.24.1.1   The Different Forms of Cannabis

Together with coffee and tobacco, Cannabis is the most commonly used psychoactive drug worldwide, and it is the single most popular illegal drug. Worldwide over 160 million people are using Cannabis regularly and these numbers are still rising.[1] With such high popular demand, it is not surprising that Cannabis and its products are known under a large variety of names. Some of the most widely used ones are defined here.

The commonly used term 'marijuana' or 'marihuana' traditionally describes the Cannabis plant when used as a recreational drug, and is frequently associated with the negative effects or social impact of the drug. 'Weed' is another name for Cannabis when used as a recreational drug. In contrast, when the term 'hemp' is used, it usually refers to the use of Cannabis as a source of fiber, making the term fiber-hemp therefore somewhat superfluous. Because of the inexact and unscientific nature of these terms, they will not be used in this chapter. Instead, the proper scientific name 'Cannabis' will be consistently used to describe the plant *C. sativa* L. in all its varieties.

When discussing about Cannabis for recreational, medicinal, or scientific use, what is usually referred to are the female flowers (also known under the Latin name *flos*), being the most potent part of the plant. The dried resin obtained from these flowers is generally known as 'hash', or 'hashish', although a large variety of names exist throughout the world. This resin is the source of the most important bioactive components of the Cannabis plant, the cannabinoids, which will be the main focus throughout this chapter.

Finally, 'dronabinol' is another name for the naturally occurring (−)-*trans*-isomer of THC, often used in a medical context in the scientific and political literature, and adopted by the World Health Organization.

3.24.1.2   The Botany of *Cannabis sativa*

The basic material of all Cannabis products is the plant *C. sativa* L. (**Figure 1**). It is an annual, usually dioecious, more rarely monoecious, wind-pollinated herb, with male and female flowers developing on separate plants. It propagates from seed, grows vigorously in open sunny environments with well-drained soils, and has an abundant need for nutrients and water. It can reach up to 5 m (16 ft) in height in a 4–6-month growing season. However, in modern breeding and cultivation of recreational Cannabis, the preferred way to propagate the plants is by cloning, using cuttings of the so-called mother plant. As this term indicates, female plants are used for this purpose, as they produce significantly higher amounts of psychoactive compounds than the male plants.

The sexes of Cannabis are anatomically indistinguishable before they start flowering, but after that, the development of male and female plants varies greatly. Shorter days, or more accurately longer nights, induce the plant to start flowering.[2] The female plant then produces several crowded clusters of individual flowers (flower tops); a large one at the top of the stem and several smaller ones on each branch, whereas the male

Figure 1 *Cannabis sativa*. A female plant in full bloom. Photo courtesy by Bedrocan BV, The Netherlands.

flowers hang in loose clusters along a relatively leafless upright branch. The male plants finish shedding their pollen and die before the seeds in the female plants ripen, that is 4–8 weeks after being fertilized. A large female can produce over 1 kg of seed. If the seed survives, it may germinate the next spring.

According to current botanical classification, Cannabis belongs, only with *Humulus* (hops), to the small family of Cannabinaceae (also Cannabaceae or Cannabidaceae).[3–5] Despite this close relationship, cannabinoids (see Section 3.24.2.1) can only be found in *C. sativa*. In the genus *Humulus*, even in grafting experiments between *Cannabis* and *Humulus*, no cannabinoids have been found,[6,7] but instead a variety of the so-called bitter acids, such as humulone, adhumulone, and cohumulone are produced. The close relationship between both plant species is clearly shown by the fact that both compounds (cannabinoids and bitter acids, respectively) are derived from similar biosynthetic pathways (see Section 3.24.2.2). Furthermore, both are excreted as a resinous mixture by glandular hairs, mainly found on female flowers.

The current systematic classification of Cannabis is:[8]

Division Angiosperms
Class Dicotyledon
Subclass Archichlamydeae
Order Urticales
Family Cannabinaceae
Genus *Cannabis*
Species *sativa* L.

Because of centuries of breeding and selection, a large variation of cultivated varieties (or cultivars) has been developed. Already, more than 700 different cultivars have been described[9] and many more are thought to exist. As a result, there has been extensive discussion about further botanical and chemotaxonomic classification. So